Stereocontrolled Glycosyl Transfer Reactions with Unprotected Glycosyl Donors

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Received May 10, 2000

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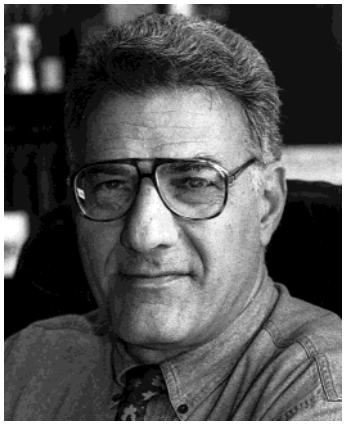
I. Introduction

It has long been acknowledged that "half of sugar chemistry resides at the anomeric carbon atom". Indeed, soon after the total synthesis of glucose by Emil Fischer,[1] he demonstrated the unique properties of the hemiacetal function by an acid-catalyzed condensation reaction with methanol to give the corresponding methyl glucoside. We now know this method as the Fischer glycoside synthesis.[2] Remarkably, there was no need for protective groups, as more than often is the case today in such transformations. Equally remarkable in the context of late 19th century milestones in organic synthesis was the first synthesis of a phenolic glycoside from sodium phenoxide and "acetobromoglucose" by Michael.[3] It is of historical interest that this base-catalyzed glycoside synthesis preceded Fischer by a few years. Since then, generations of 20th century carbohydrate chemists have instinctively and steadily contributed to the art and the science of glycoside synthesis while experiencing many challenges. Today, the total synthesis of an oligosaccharide comprising over a dozen sugar units can be achieved in relatively good yields and with impressive stereocontrol, especially under optimized conditions.[4] Enormous progress has also been made in the enzyme-mediated synthesis of oligosaccharides and glycopeptides.[5]

The ever-increasing importance of the role of carbohydrates in biological processes relating to immunology, virology, cancer, antibiotic action, and a host of life-threatening diseases has heightened the interest in the accessibility of specific sugar-based molecules.[6] Newer methods of stereocontrolled glycoside synthesis, including oligosaccharides,[7] have been a source of great challenge and inspiration for several decades since the venerable Koenigs−Knorr method and its modified versions.[8] The prospects of declaring an oligosaccharide as a drug candidate which envisages the ability to produce kilogram quantities of material is not as far-fetched as it was two decades ago. Indeed, improvements in chemical and enzymatic methods of oligosaccharide synthesis have rendered this once onerous task feasible on large scale.[9]

Despite great advances, the stereocontrolled synthesis of glycosides with a desired anomeric orientation of a particular alcohol aglycone remains out of the realm of a universal method. For masked within

10.1021/cr9903454 CCC: $35.00
Published on Web 11/10/2000



Stephen Hanessian holds the Medicinal Chemistry Chair at the Université de Montréal. He obtained his Ph.D. degree from The Ohio State University in 1960 then joined the Parke-Davis Research Laboratories in Ann Arbor, MI, as a research chemist where he remained until he moved to Montreal in 1968. He is the author of close to 400 publications and 25 patents. His research interests span a wide cross-section of areas related to organic, bioorganic, and medicinal chemistry.

Boliang Lou was born in China in 1963. He studied chemistry at Ningbo Normal College and received his M.S. degree (1986) and Ph.D. degree in Organic Chemistry (1989) from the Shanghai Institute of Organic Chemistry (SIOC) with Professor Li-Xin Dai. He was the first recipient of the President Graduate Award in the Chinese Academy of Science. From 1990 to 1994, he was engaged in postdoctoral research with Professor Stephen Hanessian at the University of Montreal. In 1994 he joined Cytel Corporation, CA, as a Staff Scientist where his primary focus was the discovery and development of small carbohydrate molecules as antiinflammatory drugs. He began work on combinatorial chemistry after joining Ontogen Corporation, CA, in 1996. One year later he moved to Helios Pharmaceutical (now Advanced SynTech) as Staff Researcher II and became the Research Section Head of Chemistry in 1998. He currently directs and manages the Department of Chemistry working in the area of combinatorial and high-throughput discovery chemistry.

a given hexose, for example, are many electronic, steric, spatial, orientational, conformational, and reactivity features that differ from one diastereomer to another. As an example, the sometimes "unpredictable" behavior of D-glucose versus D-galactose in manipulating their hydroxyl groups (e.g., displacements at C-6)[10] and in glycoside synthesis (e.g., anomeric configuration) can be a source of frustration as well as a challenge. In this regard, sugars are definitely "different" than other classes of abundant natural compounds (e.g., amino acids or lipids).

This paper is devoted principally to reviewing methods of *O*-glycoside synthesis from anomerically activated glycosyl donors in which minimal or no hydroxyl protection is needed. In other words, Fischer glycosylation of alcohols is revisited over 100 years later and nature's pathways to glycoside synthesis are emulated albeit with limitations. We also review the concept of remote activation in glycosyl transfer reactions as exemplified by the chemistry of *O*-unprotected 3-methoxy-2-pyridyloxy (MOP) glycosyl donors.

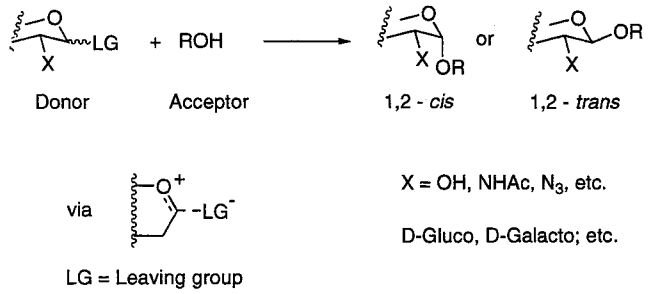


Figure 1. Challenges in the formation of the glycosidic bond.

II. Challenges of Glycoside Synthesis

The union of a glycosyl donor and an alcohol (glycosyl acceptor) presents major challenges as listed in Figure 1: (a) stereoselectivity for 1,2-*cis*- or 1,2-*trans*-glycosidic bonds; (b) site-selectivity traditionally achievable by selective *O*-protecting strategy in the acceptor; (c) protection and deprotection of hydroxy groups in donor and acceptor molecules (heavily practiced in the synthesis of oligosaccharides); (d) structure specificity (e.g., the stereoselectivity and chemical yield can depend on the nature of the glycosyl donors or acceptors); (e) formation of a specific type of glycosidic bond (e.g., sialyl glycosides, 2-deoxy glycosides, etc); (f) sequential assembly of oligosaccharides in solution and on solid support.

Some of the above challenges are addressed by the classical approaches to glycoside synthesis that rely on activation of suitably protected glycosyl donors (e.g., esters, ethers) and selectively protected acceptors. For example, the Koenigs−Knorr method[8] affords 1,2-*trans*-glycosides from the corresponding peracylated glycosyl halides in the presence of a heavy-metal salt. The method became more practical in the synthesis of oligosaccharides upon the introduction of silver triflate as an activator in the mid-1970s.[11] Glycosyl halides containing a nonparticipating benzyl group at the C-2 position lead to 1,2-*cis*-glycosides via the halide ion-catalyzed protocol described by Lemieux.[12] However, the broad application of these methods can be limited as the structures of the oligosaccharides increase in complexity. Therefore, a significant effort has been made toward designing novel anomeric leaving groups in order to overcome these limitations.

III. Brief Survey of Post-1980 Methods of Anomeric Activation

1. Non-Bromide, -Chloride, -Iodide Methods for Anomeric Activation

Glycosyl trichloracetimidates introduced by Schmidt[13] are easily prepared from the corresponding

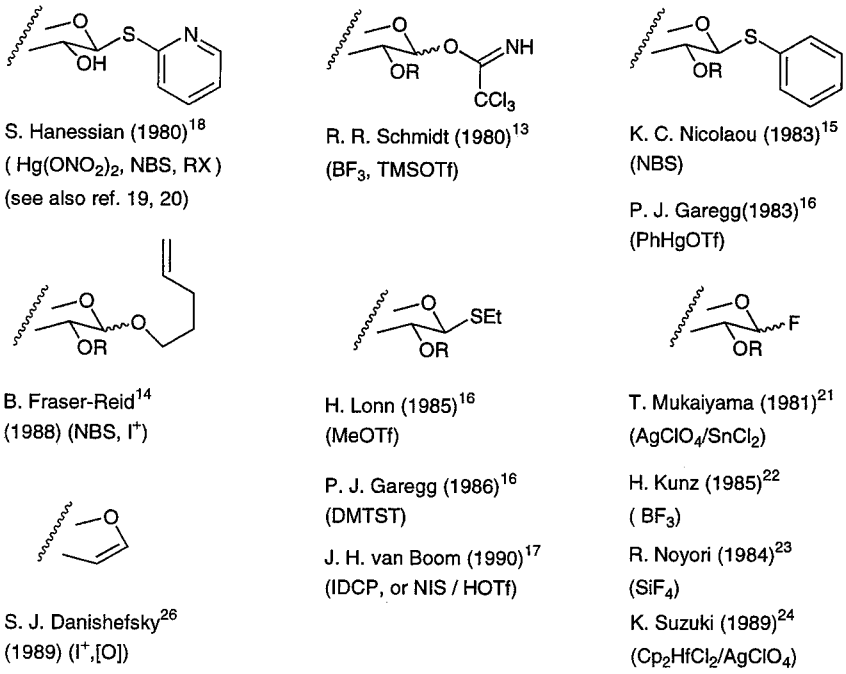


Figure 2. Selected post-1980 anomeric leaving groups and activation methods.

O-substituted reducing sugars, and they can be readily activated by Lewis acids such as BF_3 and TMSOTf under mild conditions (Figure 2). Numerous applications to oligosaccharide synthesis are reported. Due to the relative lability of the trichloroacetimidate leaving group, prolonged storage or chromatography is normally avoided.

n-Pentenyl glycosyl donors developed by Fraser-Reid[14] can be activated by electrophilic reagents such as NIS. The reaction may be accelerated in the presence of TfOH or TMSOTf which catalyze the heterolysis of NIS to generate iodonium ion. The method has found applications in the synthesis of some complex 1,6-linked oligosaccharides using an iterative strategy where the nature of the protecting groups (benzyl vs acyl) determines the resultant anomeric configuration of the major products.

Activation of thioglycosides[15−17] with thiophilic reagents is often used in the synthesis of oligosaccharides. Since the alkylthio groups are stable under most protection and deprotection conditions, they can be present during routine manipulations of the donors, unlike glycosyl imidates and bromides which are preferably prepared just before the glycosylation step. Thioglycosides are activated by various thiophilic agents, such as NBS, PhHgOTf, single electron-transfer reagents, MeOTf, dimethyl(methylthio)-sulfonium triflate (DMTST), iodonium dicollidine perchlorate (IDCP), NIS, $TrClO_4$, etc. Despite their versatility, the use of thioglycosides as donors in multikilogram-scale oligosaccharide synthesis may be hampered by the toxic nature of the reagents and the promoters. 2-Pyridylthioglycosides have found utility as unprotected[18] and protected glycosyl donors in the synthesis of *C*-glycosides[19] and *O*-glycosides.[20]

Glycosyl fluorides are often used as glycosyl donors which can be activated by strong Lewis acids, such as $AgClO_4/SnCl_2$,[21] BF_3,[22] SiF_4,[23] and $Cp_2HfCl_2/AgClO_4$.[24] Application of the fluoride method to complex oligosaccharide synthesis has been shown by its combination with thioglycoside activation in a two-stage activation procedure developed by Nicolaou and co-workers.[25]

Glycals are readily accessible and can react with a wide range of electrophilic reagents via the corresponding oxocarbenium ion.[26] Danishefsky and co-workers[27] reported a method for the stereoselective epoxidation of a glycal followed by ring opening at the anomeric position by nucleophilic attack in the presence of an appropriate Lewis acid, forming a 1,2-*trans*-glycoside with high selectivity. Further exploratory work conducted by the same group demonstrated the potential of this method for the syntheses of biologically important carbohydrates[28] and its extension to solid-phase oligosaccharides synthesis.[29]

2. New Generations of Anomeric Leaving Groups and Activation Methods

Efforts have continued toward developing more highly efficient new glycosylation methods during the past decade. Figure 3 shows representative examples of new anomeric leaving groups reported during the last two decades.

According to Kahne,[30] anomeric sulfoxides can be activated in the presence of triflic anhydride. The method has been particularly useful for the glycosylation of unreactive hydroxy groups in acceptors, and it is compatible to polymer-supported glycosylation.[31] Insights into the nature of the reactive intermediate have been proposed.[32]

Glycosyl 2-propenyl carbonates were introduced by Sinaÿ[33] for the stereocontrolled formation of 1,2-*trans*-glycosidic linkages even in the absence of neighboring participating groups at C-2 position of the donors. A number of glycosylation methods using glycosyl phosphites,[34] glycosyl phosphates,[35] and glycosyl iodides[35c] as donors were recently reported.

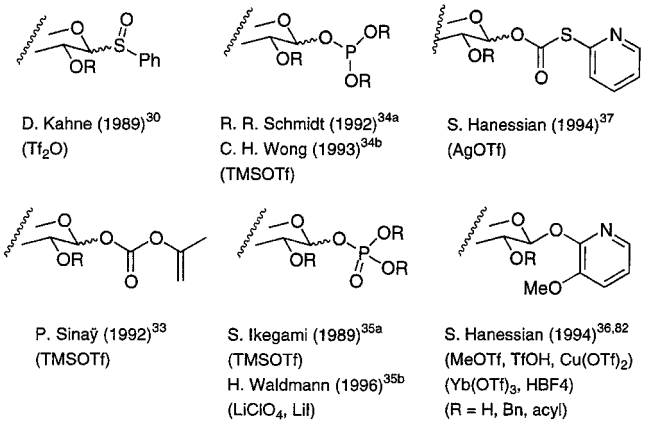


Figure 3. New generations of anomeric leaving groups and activation methods.

The design and utilization of the 3-methoxy-2-pyridyloxy (MOP) group[36] will be discussed below. The use of 2-pyridylthiocarbonates as leaving groups in conjunction with *O*-protected glycosyl donors has been reported elsewhere.[37]

IV. Glycosylation with Unprotected Glycosyl Donors

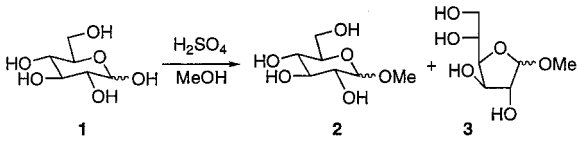
1. *O*-Glycosides

The chemical synthesis of oligosaccharides has, so far, heavily relied on the use of *O*-protected glycosyl donors in block or stepwise fashion. Regioselectivity in glycosylation is usually achieved by the differentiation of hydroxyl groups by selective protection keeping a single position available on the acceptor for glycosidic bond formation. In this regard the notion of glycoside synthesis with *unprotected* donors may have enormous appeal and obvious practical value for the following important reasons: (a) the number of steps in glycoside synthesis can be reduced; (b) glycosylation of simple and complex aglycones without the need for protection of the hydroxyl groups in the donor (e.g., macrolide antibiotics); (c) unprotected glycosyl donors could possess higher reactivity compared to the *O*-acyl-protected ones because of the absence of electronic effects caused by the ester groups; (d) the stereochemistry of the glycosidic bond could be different owing to the absence of protective groups; (e) possibilty for iterative assembly of saccharide moieties; (f) potential for extension to solid-phase synthesis of glycosides avoiding protection−deprotection steps.

Glycosylation with an *unprotected* glycosyl donor presents major challenges and problems, namely, (a) the glycosyl donor should be easily accessible; (b) the glycosylation reaction should be fairly general for a variety of alcohol and sugar acceptors; (c) the reaction should be effective with a choice of reagents or catalysts in a reasonably short time period; (d) the glycosyl donors should react only with the hydroxyl group on the acceptor in order to avoid self-condensation; (e) the anomeric configuration of the newly formed bond should be reasonably well controlled.

Despite the tremendous progress made in the field of glycoside synthesis during the past century, it is interesting that the original Fischer method is still the method most utilized for simple alcohols (Scheme 1). By its very nature, it is mostly applicable to lower

Scheme 1. Fischer Glycosylation Method

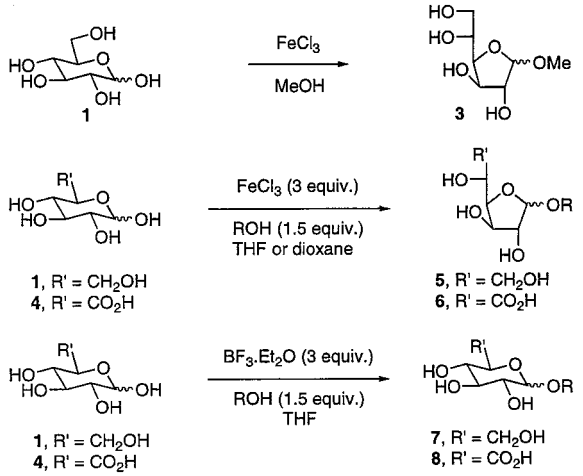


alcohols and usually leads to the thermodynamically stable anomers, produced directly or via anomerization of a kinetic product. By varying the temperature, alkyl pyranosides **2** or alkyl furanosides **3** can be obtained. Clearly, "solid" alcohols or other sugar derivatives cannot be used as nucleophiles (acceptors) in a Fischer glycosylation. Any prospects of utilizing unprotected glycosyl derivatives as donors must take into account the need to generate an oxocarbenium ion or its reactive equivalent. Nature, of course, engages in glycoside synthesis through the activation of its donors as nucleotides and the intermediacy of glycosyl transferases. The challenge then is to devise suitable groups at the anomeric center of a glycosyl donor that can be induced to leave while creating oxocarbenium ion character. If the activatable group is stereochemically defined in the donor, then an S_N2-like reaction with an alcohol can lead to the glycoside "with inversion" of anomeric configuration, otherwise mixtures of anomeric glycosides will be formed.

A. Fischer-type Glycosylation of Alcohols

It took an entire century to replace a protic acid in the original Fischer glycosylation of simple alcohols by a Lewis acid! Encouraged by the early observation of the effect of alkaline-earth metal ions on the Fischer reaction, Lubineau and Fischer[38] (no relation) treated free sugars with methanol in the presence of ferric chloride or $BF_3{\cdot}Et_2O$ (Scheme 2). Thus, D-

Scheme 2. Modified Fischer Method



glucose and D-galactose were treated with ferric chloride in methanol at room temperature or 60 °C, respectively, to give the corresponding methyl α,β-D-glucofuranosides and methyl α,β-D-galactofuranosides exclusively in 75% yield. The results indicated

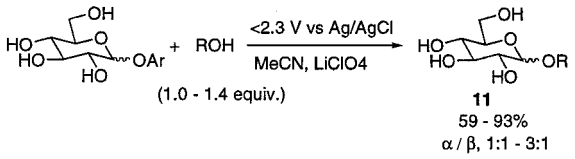
that the ring expansion to pyranosides is prevented by the presence of ferric ions in the reaction mixture.

Plusquellec and co-workers[39] adapted a similar approach but using only 1.5 equiv of alcohol and THF or dioxane as solvent (Scheme 2). A general observation was that the *O*-glycosylation of reducing sugars such as D-glucose, D-galactose, D-mannose, and even D-galacturonic acid, in the presence of anhydrous ferric chloride, afforded furanosides in good to excellent yields. Alkyl α-pyranosides were obtained from D-glucose, D-mannose, *N*-acetyl-D-glucosamine, and D-galacturonic acid in the presence of $BF_3 \cdot Et_2O$.

B. Miscellaneous Methods

Noyori and co-workers[40] reported an electrochemical glycosylation method using unprotected phenolic D-glucopyranosides such as **9** or **10** which react with simple alcohols (1−2 equiv) under mild electrolytic conditions to give the corresponding *O*-alkyl D-glucopyranosides **11** in good yield but with low anomeric selectivity (Scheme 3). This method was also adapted

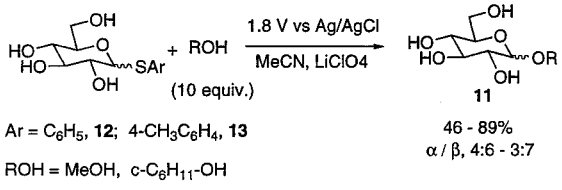
Scheme 3. Electrochemical Glycosylation Method[a]



[a] Ar = C_6H_5, **9**; 2,4,6-$(CH_3)_3C_6H_2$, **10**. ROH = MeOH, EtOH, t-BuOH, c-C_6H_{11}−OH, Me_3CCH_2OH.

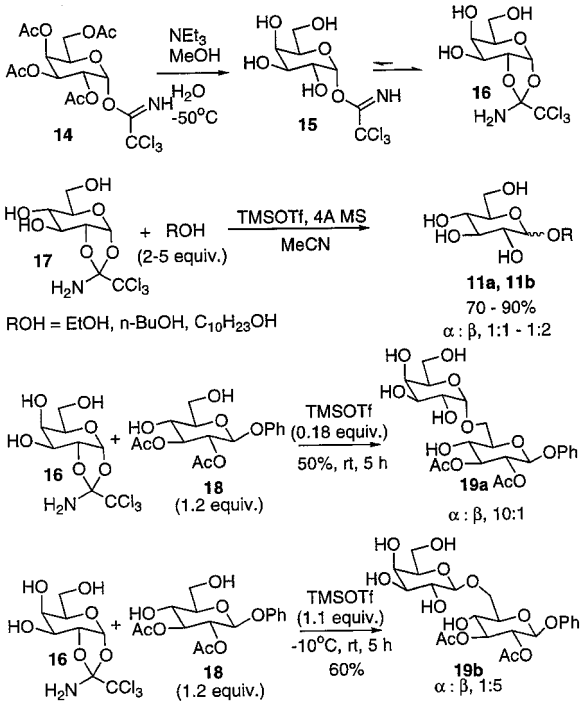
to unprotected aryl thioglycosides, such as **12** and **13**, but at a lower oxidation potential (Scheme 4).[41]

Scheme 4. Electrochemical Glycosylation Method



Attempts to prepare unprotected glycosyl trichloroacetimidates in order to investigate their potential in glycoside synthesis were not successful (Scheme 5). Deacetylation of peracetylated α-glycosyl trichloroacetimidates under various basic conditions did not afford the desired unprotected glycosyl trichloroacetimidate.[42] Careful NMR analysis revealed that the major products were 1,2-trichloromethyl orthoamides, which was confirmed by X-ray crystallography. Scheme 5 shows examples of the attempted glycosylation with unprotected glycosyl donors prepared from the corresponding peracetylated D-galactopyranosyl trichloroacetimidate, **14**. The synthesis of disaccharides such as **19a** and **19b** is possible, but the anomeric selectivity can vary depending on the temperature. Reaction with acetic acid in the presence of a catalytic amount of TMSOTf gave glycosyl acetates. Orthoamide (amide acetal) derivatives of alcohols, *cis*-diols, including sugars have been previously used as nucleophiles in conjunction with Lewis acid-catalyzed reactions of peracylated glycosyl donors to give the corresponding 1,2-*trans*-glycosides

Scheme 5. Attempted Glycosylation with Unprotected Glycosyl Imidate



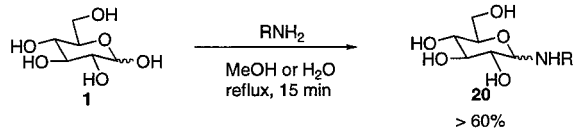
or disaccharides.[43a−c] Alternatively, 1,2-orthoamide analogues of benzylated sugars could be used as glycosyl donors in the presence of an alcohol acceptor by activation with methyl iodide to give a the trimethylammonium acetal.[43d]

2. Glycosylamines and Glycosyl Azides

Like the Fischer glycoside synthesis, the aminolysis of free sugars was studied more than a century ago, and progress in this area has been well documented in several review articles.[44]

Simple *N*-alkyl glycopyranosylamines **20** can be prepared as a mixture of α/β isomers from the corresponding unprotected aldoses by heating with various amines in water or methanol (Scheme 6).[45]

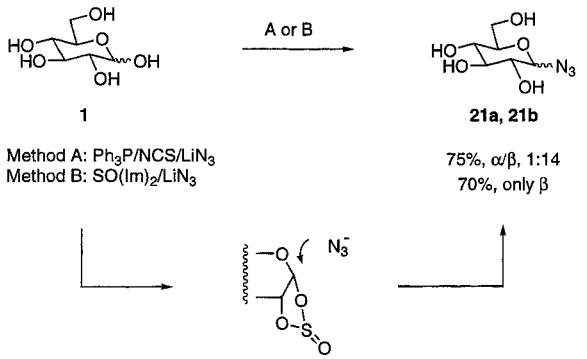
Scheme 6. Preparation of Glycosylamines



Caution should be excercised in the synthesis of *N*-glycosides due to their lability toward hydrolysis under either acidic or basic conditions. Interestingly, acylation of a mixture of α/β glycosylamines often leads to a single anomer because of anomerization.[46]

Glycosylamines can also be prepared from the corresponding glycosyl azides.[47] This approach has now become the most practical way to generate *N*-linked glycosides with the desired stereoselectivity. Several reports have addressed the issue of stereocontrolled formation of glycosyl azides using *O*-protected glycosyl donors.[48] Very few examples have dealt with the direct formation of unprotected glycosyl azides. As shown in Scheme 7, the azidation of

Scheme 7. Preparation of Glycosyl Azides



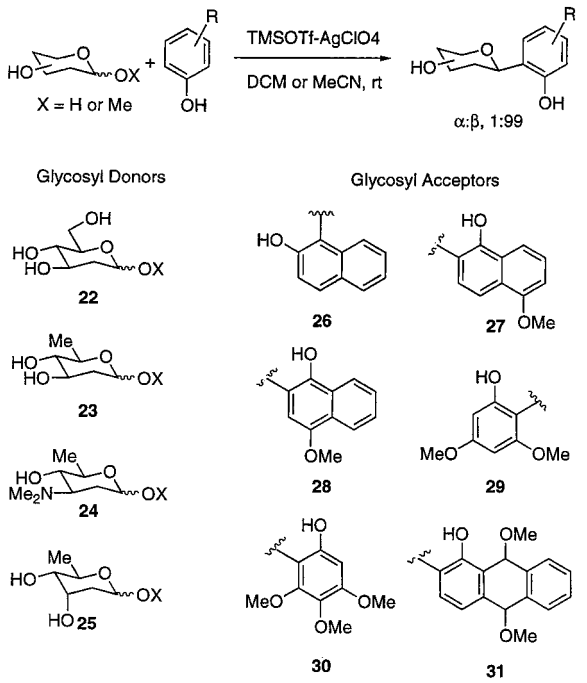
unprotected D-glucose with Ph_3P, *N*-chlorosuccinimide, and LiN_3 gives the corresponding unprotected α/β-glucosyl azides **21a** and **21b** in moderate to good yields.[49] Activation of the anomeric hydroxyl group by Ph_3P forms an alkoxyphosphonium intermediate which is then attacked by azide anion from both α- and β-faces. A one-pot stereoselective synthesis of β-glucosyl azides from the corresponding unprotected glucose, via the corresponding 1,2-cylic sulfite, has been reported[50] (Scheme 7).

3. *C*-Glycosides

Numerous biologically important aryl *C*-glycosides have been isolated and identified.[51] The development of efficient and stereocontrolled *C*-glycosylations has been an area of interest for many years.[52] However, direct *C*-glycosylation using unprotected sugar donors has few precedents.

Toshima and co-workers[53] developed highly stereoselective aryl and allyl *C*-glycosiylation methods using unprotected sugars as glycosyl donors in the presence of phenols and a Lewis acid. As shown in Scheme 8, unprotected 2-deoxy aldoses or methyl

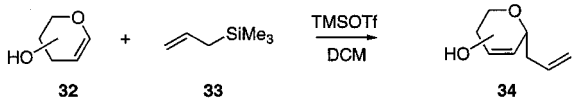
Scheme 8. *C*-Glycosylation Using Unprotected 2-Deoxy Sugars



2-deoxy-glycopyranosides (**22**−**25**) react with phenol or naphthol derivatives in the presence of TMSOTf-$AgClO_4$ or only TMSOTf to give the corresponding unprotected *o*-hydroxyaryl β-*C*-glycosides **26**−**31** exclusively in good yields. Use of the combined system (TMSOTf−$AgClO_4$) usually affords a better yield than using TMSOTf alone. The active promoter in the case of TMSOTf−$AgClO_4$ is presumably $TMSClO_4$ and/or $HClO_4$, which is generated in the presence of the free hydroxyl groups of the glycosyl donors. Triflic acid may be the activating species when TMSOTf is used.

A method for allyl C-glycosylation of unprotected glycals was reported by the same group.[53a,d] This was achieved by using allyltrimethylsilane in the presence of TMSOTf to give the corresponding unprotected 2,3-unsaturated allyl α-*C*-glycoside **34** in high yields as shown in Scheme 9. Compared to the

Scheme 9. *C*-Glycosylation Using Unprotected Glycals



corresponding acyl protected glycal, the reactions with unprotected donors proceeded much more efficiently, resulting in higher α-stereoselectivity and better yields.

The mechanistic pathway of the above-mentioned *C*-glycosylations still remains to be investigated. It is of interest that the formation of the *C*-glycosidic bond is more favorable than the self-condensation of unprotected glycosyl donors. Presumably, any phenolic glycosides formed in situ are cleaved in the presence of strong Lewis acid catalysts. Alternatively, the formation of the anomeric carbon−carbon bond could be faster than that of the *O*-glycosidic bond as proposed by Toshima and co-workers.[53a]

V. Remote Activation Concept

A common mechanistic feature of the traditional glycosylations, including the pioneering Fischer method,[2] is the direct activation of the anomeric substituent by the activator/promoter. This leads to a dissociation with the concomitant formation of an ion-paired oxocarbenium ion or a dioxolenium ion in the case of neighboring group participation.[54] Subsequent attack of the hydroxyl group of the glycosyl acceptor at the anomeric carbon forms the desired glycosidic linkage. Therefore, the dissociation of the anomeric substituent in the glycosyl donor by direct activation depends on its inherent electrofugal character, especially in the presence of a promoter.

The concept of remote activation was proposed and put into practice in the design of novel anomeric leaving groups in our laboratory more than 20 years ago.[18] The conceptual basis is that the activation of the anomeric group is triggered by an interaction of a promoter and an atom which is not directly attached to the anomeric center. As shown in Figure 4, an anomeric substituent containing two heteroatoms, X and Y, can be activated at the remote atom

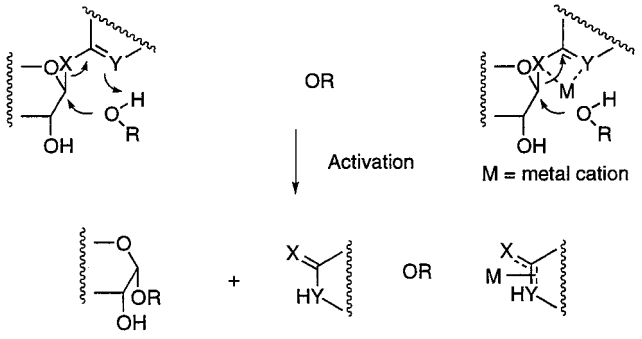
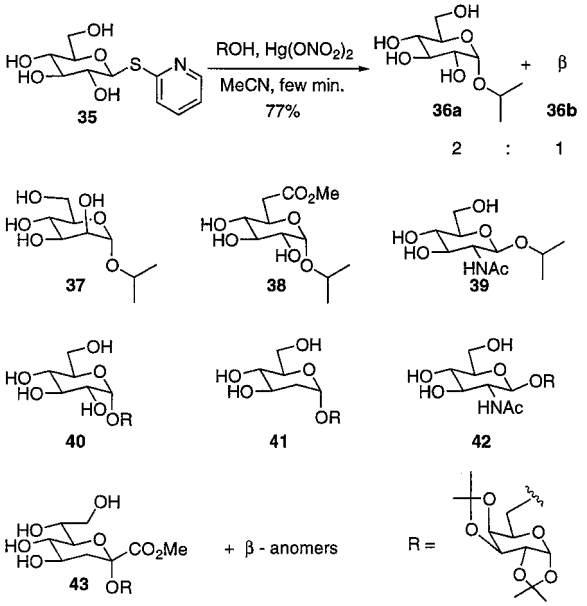


Figure 4. Remote activation concept.

Y by an electrophilic species or a metal cation. A reactive intermediate, such as an ion pair or loose complex, may be formed, which could undergo an S_N2-like attack by the hydroxyl group of the acceptor resulting in the formation of a glycoside with an apparent inversion of anomeric configuration. It was surmised that a 2-pyridylthio glycoside (Figure 4, X = S; Y = N) could fulfill these functional and electronic requirements when activated with appropriate electrophilic reagents.[18]

Thus, 2-pyridylthio β-D-glucopyranoside **35** reacted with a variety of alcohols in the presence of mercuric nitrate in acetonitrile solution, within a few minutes, to give the desired alkyl α-D-glucopyranosides as the major anomers (Scheme 10). Ferrier and co-workers[55]

Scheme 10. Glycoside Formation Using an Unprotected Glycosyl Donor by Remote Activation



reported that treatment of phenylthio α-D-glucopyranoside with a simple alcohol, such as 2-propanol, and mercuric chloride at reflux for 96 h gave a 55% yield of the corresponding α-glycoside **36a**. The notably faster glycosylations with 2-pyridylthio glycosides[18] validated the original design of this leaving group and the importance of the nitrogen atom in the pyridyl ring. Glycoside synthesis was also possible in the presence of NBS or alkyl halides such as 1-chloropentane.[18]

This concept-based *O*-glycosylation method has also been successfully applied to the synthesis of carbohydrate-containing complex antibiotics, such as erythromycin[56] and avermectin B_{1a}.[57,58] Interestingly, glycosylation of erythronolide by more traditional methods was not successful.[59]

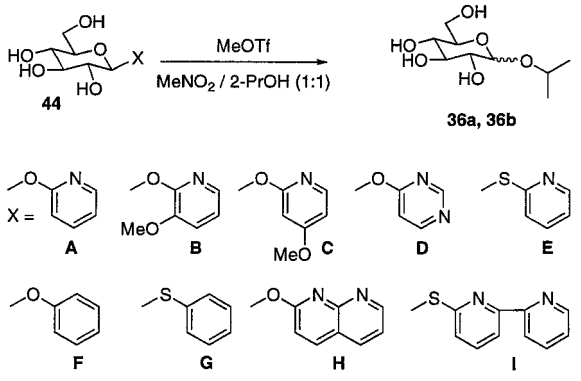
Extensions of the method to the synthesis of *O*- and *C*-glycosides with *O*-benzyl ether-protected donors were then reported by others.[19,20] It should be noted that the trichloroacetimidate[13] and pentenyl glycosyl donors[14] can also be regarded as proceeding through a remote activation, since the respective leaving groups are activated at a site not directly attached to the anomeric carbon.

VI. Stereocontrolled Glycosylation Using 3-Methoxypyridyl (MOP) O-Unprotected Glycosyl Donors

1. Design, Concept, and Activation Mechanism

The successful synthesis of *O*-alkyl glycosides and disaccharides from unprotected 2-thiopyridyl glycosides[18] prompted us to explore other anomeric leaving groups based on the remote activation concept. We examined a series of substituted heterocycles as anomeric leaving groups as shown in Table 1.[36b] A diverse set of *O*-unprotected glucopyranosyl heterocycles **A**−**I** were surveyed as donors by treatment with a stoichiometric quantity of MeOTf in a 1:1 mixture of nitromethane and 2-propanol at room temperature. Successful glycosylations were achieved in the case of **A**, **B**, **C**, and **D**. The 3-methoxy-2-pyridyloxy (MOP) group **B** was the most effective leaving group, affording 2-propyl α-D-glucopyranoside **36a** in 79% yield and excellent α/β selectivity.

Table 1. Various Heterocyclic Leaving Groups

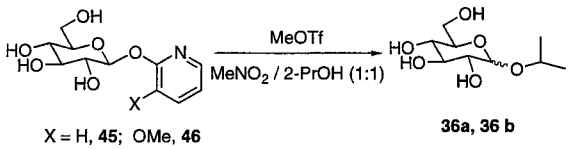


Entry	X	equiv. (MeOTf)	Time	α : β [a]	Yield (%)[b,c]
1	**A**	1.0	45 min	9 : 1	78
2	**B**	1.0	< 5 min	8 : 1	79
3	**C**	1.0	2.5 h	8 : 1	88
4	**D**	1.0	15 min	5 : 1	84

[a] The ratio was determined by ^{1}H NMR after acetylation. [b] Isolated yield. [c] Donors **E**−**I** were unreactive.

Only a catalytic amount of MeOTf was required to activate the pyridyloxy (**45**) or MOP (**46**) donors as

Table 2. A Catalytic Process



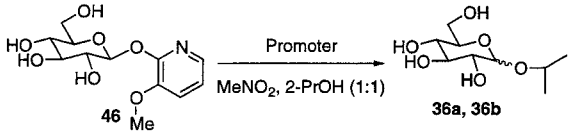
Entry	X	equiv. (MeOTf)	Time	α : β [a]	Yield (%)[b]
1	H	2	45 min	10 : 1	76
2	H	1.1	45 min	9 : 1	78
3	H	0.45	1.5 h	9 : 1	88
4	H	0.2	3 h	8 : 1	82
5	OMe	1.0	< 5 min	8 : 1	79
6	OMe	0.2	< 5 min	8 : 1	76
7	OMe	0.016	40 min	8 : 1	78

[a] The ratio was determined by ^{1}H NMR after acetylation. [b] Isolated yield.

shown in Table 2. The unprotected MOP glucosyl donor **46** was treated with a 1:1 mixture of 2-propanol and nitromethane in the presence of 0.2 equiv of MeOTf *only for 5 min* to give the corresponding glycosides with an α/β ratio of 8:1 and in 76% isolated yield after acetylation. Glycosylation with the corresponding pyridyl donor **45** was equally selective but required 3 h for completion of the reaction.

Other activating reagents, such as triflic acid, *p*-toluenesulfonic acid, $BF_3{\cdot}Et_2O$, $Cu(OTf)_2$, $ZnCl_2$, NBS, fluoroboric acid,[60] and $Yb(OTf)_3$,[61] were also examined for the same glycosylation reaction with **46** as donor as shown in Table 3, although the

Table 3. Various Promoters

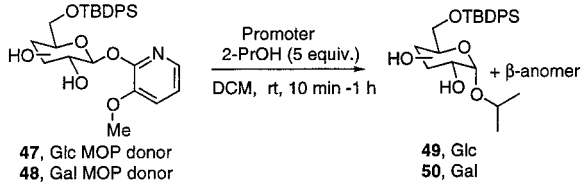


Entry	Promoter (equiv.)		Time	α : β [a]	Yield (%)[b]
1	MeOTf	(0.2)	< 5 min	8 : 1	76
2	TfOH	(0.3)	< 5 min	8 : 1	74
3	PTS	(1.0)	5 min	1 : 1	65
4	BF_3	(1.0)	5 min	8 : 1	77
5	$Cu(TfO)_2$	(1.0)	5 min	7 : 1	82
6	$ZnCl_2$	(1.0)	3 days	4 : 1	61
7	NBS	(1.0)	< 5 min	6 : 4	78
8	NBS	(0.2)	< 5 min	1 : 1	72

[a] The ratio was determined by ^{1}H NMR after acetylation. [b] Isolated yield.

reaction proceeded smoothly under most conditions, except when using a weak Lewis acid such as $ZnCl_2$ (3 days), and the stereoselectivity varied from 1:1 to 8:1. Interestingly, the reaction using triflic acid as promoter afforded similar results as with MeOTf, while the use of *p*-toluenesulfonic acid diminished the stereoselectivity considerably. Of interest was the use of only 5 equiv of alcohol when the 6-*O*-TBDPS β-pyridyl or MOP donors **47** and **48** were used (Scheme 11). Preliminary results have shown that

Scheme 11. Glycosylation Using 6-*O*-TBDPS MOP Donor[a]



[a] Promoter for **47**: $HBF_4.Et_2O$ (α: β, 2:1, 91%), s-collidine·HBF_4 (α: β, 2:1, 70%); $Cu(OTf)_2$ (α: β, 1:1, 85%), MeOTf (α: β, 2:1, 60%). Promoter for **48**: $HBF_4.Et_2O$ (α: β, 4:1, 96%), $Yb(OTf)_3$ (α: β, 3:1, 88%), $Cu(OTf)_2$ (α: β, 1:1, 73%).

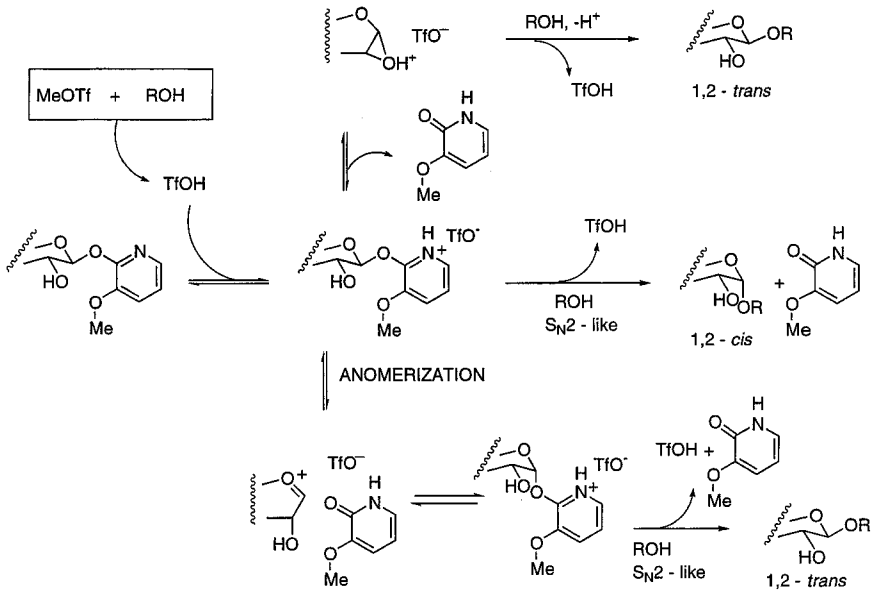
glycosides of *O*-unprotected MOP *N*-acetylneuraminic acid methyl ester can be easily prepared in the presence of MeOTf in acetonitrile using 5−40 equiv of alcohols (2-propanol, allyl alcohol, 2-hydroxy-1-benzyloxycarbonylamino ethane, sugar donors) with good anomeric selectivity.[62]

The actual species for activating the MOP leaving group in the presence of MeOTf in the glycosylation appears to be triflic acid, which is generated in situ by reaction with excess alcohol in solution. As predicated in the design of the MOP group, activation proceeds most likely through the protonation of nitrogen in the pyridine ring with TfOH to generate a tightly bound oxocarbenium ion pair species in which the β-orientated MOP group shields that side from attack by the alcohol. An S_N2-like attack from the α-face by the alcohol releases neutral 3-methoxy-2-(1*H*)-pyridone and gives the 1,2-*cis*-glycoside with regeneration of the catalyst (Scheme 12). The intermediacy of a glycosyl triflate has not been considered as part of the process.

As proposed in Scheme 12, the minor 1,2-*trans*-glycoside could arise via S_N2-type substitution from a small amount of MOP 1,2-*cis*-glycoside generated through anomerization. To confirm this hypothesis, treatment of MOP α-D-glucopyranoside with an excess of 2-propanol in the presence of MeOTf gave 2-propyl β-D-glucopyranoside predominantly (85:15, β/α) but the reaction was much slower (~45 min). 1,2-*trans*-Glycosides could also be produced through the formation of an epoxide intermediate, followed by the ring opening by the alcohol in a process resembling a double inversion at the anomeric center.

That these glycosylations proceed via a remote activation process requiring the nitrogen atom in the pyridyl ring was evident from the nonreactivity of the corresponding phenyl glycoside under the same conditions. The reactivity of the 2-pyridyloxy leaving groups also varied depending on the nature of the substituents in the ring (Table 1). The higher reactivity of the 3-methoxy-2-pyridyloxy group compared to the unsubstituted analogue, or to the much slower reacting 4-methoxy analogue, cannot be attributed to relative basicities of the pyridyl nitrogen in the donor or in the resulting 2-pyridone (intramolecular

Scheme 12. Possible Mechanistic Pathways



H-bonding of dimers). Relying on basicity alone, it is the 4-methoxy analogue that should be most reactive. It is possible that the 3-methoxy group stabilizes the incipient oxocarbenium ion in a preferred rotamer due to its proximity. It would be of interest to compare the reactivity of the corresponding 3-trifluoromethyl and related analogues.

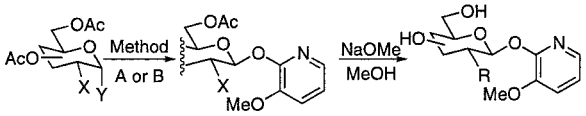
2. Preparation of MOP Glycosyl Donors

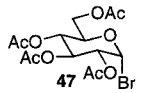
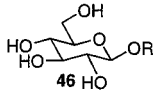
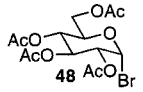
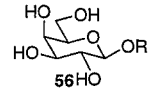
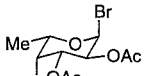
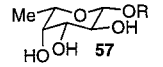
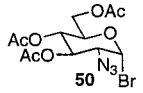
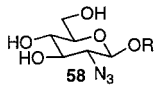
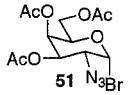
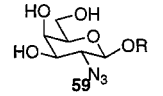
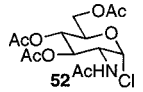
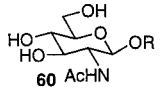
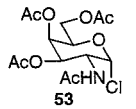
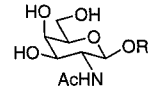
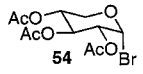
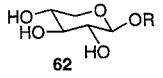
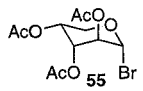
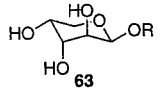
Unprotected MOP glycosyl donors are easily prepared in a multigram scale from the corresponding peracetylated glycosyl halides followed by de-*O*-acetylation. They are usually crystalline and have excellent shelf life as exemplified by MOP donors **46** and **56**−**59** as shown in Table 4. In method A, silver 3-methoxy-2-pyridoxide is used to couple the MOP group to the anomeric carbon. This heterogeneous reaction is usually performed at 100−110 °C for a short period of time. A simple filtration offers the products in good yield with the desired 1,2-*trans* anomeric configuration in the cases studied. Alternatively, the MOP group can be introduced by directly using 3-methoxy-2-(1*H*)-pyridone in the presence of a phase-transfer catalyst, such as $(hexyl)_4NHSO_4$ or Bu_4NBr, in a mixture of aqueous NaOH and dichloromethane in yields ranging from 45% to 60%.[62] The major byproduct when using this method is the corresponding MOP *N*-glycoside. This can be avoided by using 6-methyl-2-(1*H*)-pyridone, which affords the corresponding 6-methyl 2-pyridyl β-D-galactopyranoside in >65% yield.[63]

2-Acetamido glycosyl MOP donors are also prepared by method B from the corresponding peracetylated glycosyl chlorides in moderate yields (30−32%). Alternatively, they can be synthesized from the MOP 2-azido-2-deoxy β-D-glycosides. The azido group is reduced to the corresponding amine by hydrogenation, then *N*-acetylated to afford the 2-acetamido glycosides in more than 75% overall yield.

MOP α-D-galactopyranosyl and MOP α-D-glucopyranosyl donors (for example, **66**) are produced by

Table 4. Preparation of Unprotected MOP β-Glycosyl Donors

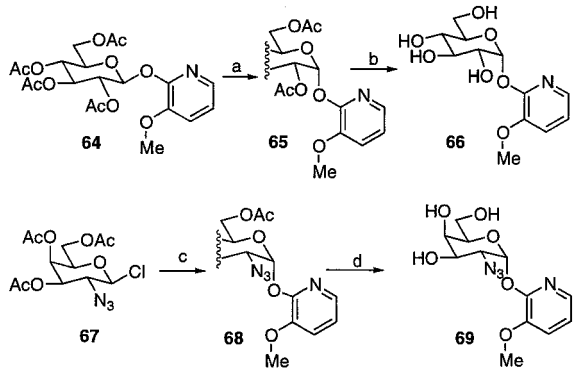


Entry	Glycosyl halide	Method[a]	MOP Donor	Yield (%)
1	 **47**	A B	 **46**	77% 53%
2	 **48**	A B	 **56**	68% 50%
3	 **49**	A B	 **57**	65% 48%
4	 **50**	A	 **58**	72%
5	 **51**	A	 **59**	63%
6	 **52**	B	 **60**	32%
7	 **53**	B	 **61**	30%
8	 **54**	B	 **62**	66%
9	 **55**	B	 **63**	45%

[a] Method A: Ag(MOP), toluene, 110 °C. Method B: 3-methoxy-2-1*H*-pyridone, aq. NaOH, Bu_4NBr or $(Hex)_4NHSO_4$, CH_2Cl_2.

anomerization of the corresponding peracetylated MOP β-glycosides in the presence of $HgBr_2$ at high temperature (Scheme 13). MOP 2-azido-2-deoxy α-D-galactopyranosyl donor **69** can be obtained in good yield by treatment of peracetyl 2-azido-2-deoxy-α-D-galactopyranosyl chloride **67** with silver 3-methoxy-2-pyridoxide, followed by deacetylation of the resulting glycoside **68**.

Scheme 13. Preparation of Unprotected MOP α-Glycosyl Donors[a]



[a] Conditions: (a) $HgBr_2$, xylene, 130 °C, 5 h. (b) NaOMe, MeOH, CH_2Cl_2, quantitative yield. (c) Ag(MOP), toluene, reflux. (d) NaOMe MeOH, 90%.

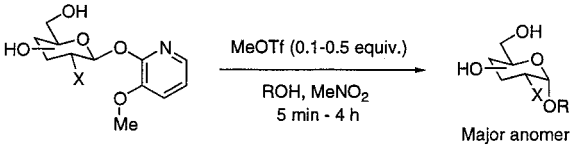
3. Glycosylation with *O*-Unprotected MOP Glycosyl Donors

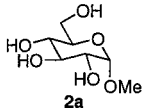
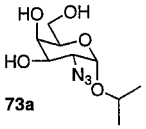
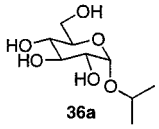
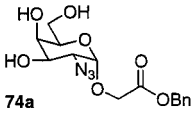
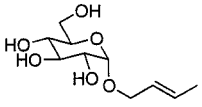
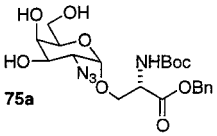
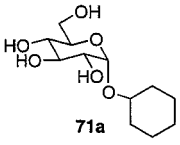
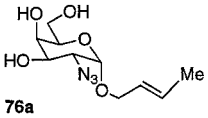
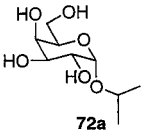
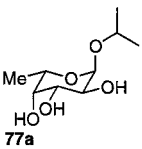
A. Synthesis of O-Glycosides and Oligosaccharides

Table 5 summarizes the results from the glycosylation of various *O*-unprotected MOP donors activated by MeOTf in the presence of an excess of alcohol. As expected, the reaction proceeded smoothly with good to excellent 1,2-*cis* stereoselectivities. The acceptor alcohol was used in excess in order to enhance the coupling process and suppress side reactions such as hydrolysis of unprotected MOP donors, 1,6-anhydro formation, and self-condensation. In the absence of alcohol, treatment of **46** with MeOTf afforded 1,6-anhydro-D-glucopyranose, anomerized D-glucosyl MOP donor, and D-glucose.

Disaccharides and trisaccharides could be prepared in the presence of an excess of a sugar acceptor (7−10 equiv). As illustrated in Table 6, glycosylation with a variety of MOP donors produced preferentially 1,2-*cis*-glycosides **83a**−**86a**, except when a 2-acetamido group was present which led to the 1,2-*trans* product **88**, presumably via the intermediacy of an oxazolinium ion. In all cases the excess of the sugar acceptors could be easily recovered through a short plug of silica gel due to a significant difference in the polarity between the products and the acceptors. An

Table 5. Glycosylation with Unprotected MOP Donors



Entry	Major Product,	%, ratio[a]	Entry	Major Product,	%, ratio[a]
1	 **2a**	82%, 10:1[b,c]	6	 **73a**	86%, 12:1[b]
2	 **36a**	76%, 8:1[b,c]	7	 **74a**	70%, 17:1
3	 **70a**	77%, 16:1[b,c]	8	 **75a**	65%, 8:1
4	 **71a**	62%, 5:1[b,c]	9	 **76a**	84%, 6:1
5	 **72a**	86 %, 12:1[b,c]	10	 **77a**	84%, 4:1[b]

[a] α/β Ratio determined by ^1H NMR at 300 MHz and confirmed by weights of isolated glycosides whenever possible. [b] 1:1 (v/v) ratio of acceptor and solvent used. [c] Yield of isolated peracetylated glycosides.

Table 6. Disaccharide Synthesis with Unprotected MOP Donors[a]

Entry	MOP Donor	Acceptor (equiv.)	Major Product	α : β[b]	Yield (%)[c]
1	**46**	**78** (10)	**83a**	4 : 1	61
2	**46**	**79** (7)	**84a**	2.4 : 1	42
3	**55**	**80** (7)	**85a**	α-only	43
4	**55**	**81** (7)	**86a**	α-only	**56**
5	**57**	**78** (14)	**87a**	8 : 1	77
6	**57**	**82** (14)	**88**	β-only	68

[a] R,R = cyclohexylidene. [b] Ratio determined by ^{1}H NMR at 300 MHz and confirmed by weights of isolated glycosides whenever possible. [c] Yield of isolated, chromatographically pure glycosides.

operational amenity is the ability to follow the progress of all MOP and related glycosylations by monitoring the formation of the UV-absorbing 3-methoxy-2-(1*H*)-pyridone by TLC (Scheme 12).

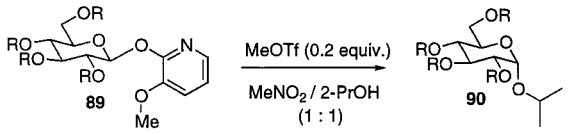
B. Selective Activation

In further investigating the versatility of the MOP leaving group and exploiting its potential for the synthesis of biologically important oligosaccharides, it was found that introduction of any protecting group on the unprotected MOP glycosyl donors resulted in a significant decrease of the reactivity. As shown in Table 7, various MOP glycosyl donors with *O*-protective groups, such as *tert*-butyldimethylsilyl, benzyl, or benzoyl, were treated with of 0.2 equiv of MeOTf in $MeNO_2$/2-propanol. Completion of the glycosylation with MOP 6-*O*-TBDMS-*β*-D-glucopyranoside **91** and MOP 2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranoside **94** required 20 min and 5 h, respectively, compared to a few minutes when the unprotected MOP **46** donor was used. Most important was the finding that *O*-acyl-protected MOP glycosides such as **95** are practically unreactive in the presence of MeOTf.

The observed deactivation of the anomeric center by *O*-protection can be attributed to an electronic effect, particularly when esters are present.[64] The electron-withdrawing effect of such esters is unfavorable in its ability to stabilize an incipient oxocarbenium ion generated by the activation of the leaving group under aprotic acidic conditions. The propensity of protonated pyridinium species may also be diminished due to this electronic effect. Studies on the difference of chemical shifts of anomeric protons and carbons based on the ^{1}H NMR and ^{13}C NMR spectra of a variety of MOP glycosyl donors further support the above proposals (Table 8). The chemical shifts of the anomeric proton of all the unprotected MOP donors tend to appear at higher field compared with the corresponding partially and fully protected donors. In contrast, the ^{13}C chemical shifts of the anomeric carbon of all the unprotected MOP unprotected donors appeared at lower field compared to the corresponding *O*-protected donors. In both cases, a significant difference between unprotected and *O*-acylated MOP glycosides was observed.

The selective activation of *O*-unprotected MOP glycosyl donors can be achieved in the presence of partially esterified MOP glycosyl acceptors to give oligosaccharides. Table 9 illustrates examples of this strategy using unprotected MOP donors and partially *p*-fluorobenzoylated MOP acceptors in the presence of catalytic amounts of MeOTf. The reactions proceeded smoothly in DMF as solvent to give di- and trisaccharides such as **109**−**115** with 1,3- and 1,6-linkages in reasonable to good yields and with 1,2-

Table 7. Comparison of Unprotected MOP Glycosyl Donors with Protected MOP Glycosyl Donors



89 90

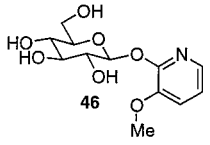
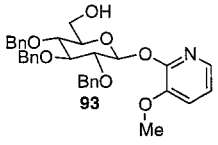
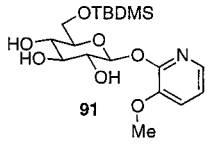
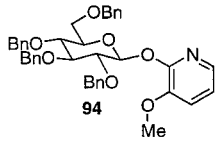
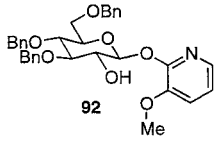
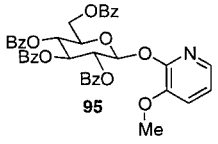
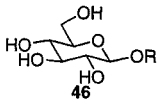
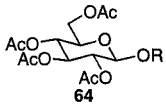
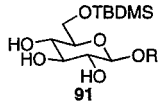
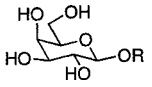
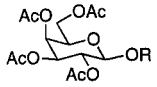
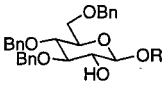
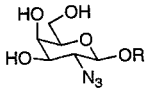
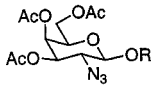
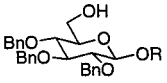
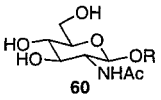
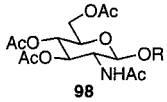
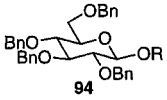
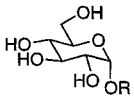
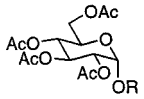
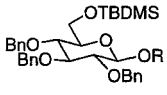
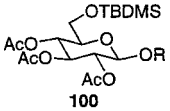
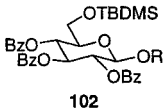
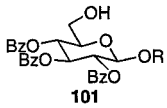
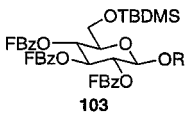
MOP-Glycosides	Time	α : β	Yield(%)	MOP-Glycosides	Time	α : β	Yield(%)
 46	< 5 min	8 : 1	76	 93	2 h	only α	95
 91	20 min	9 : 1	84	 94	5 h	only α	85
 92	1 h	5 : 1	88	 95	5 h	No reaction	

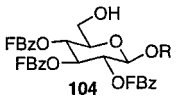
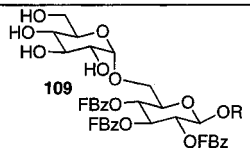
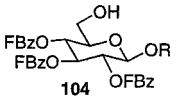
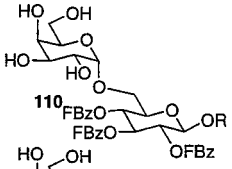
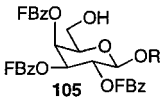
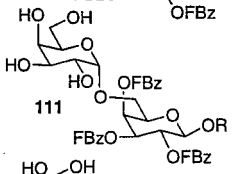
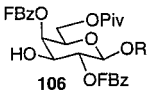
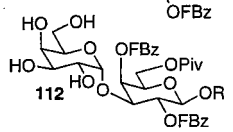
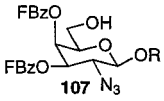
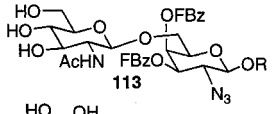
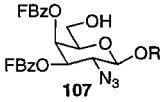
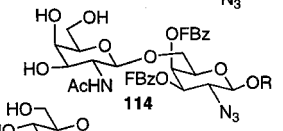
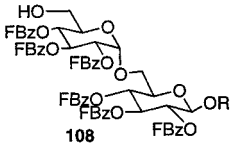
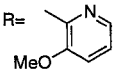
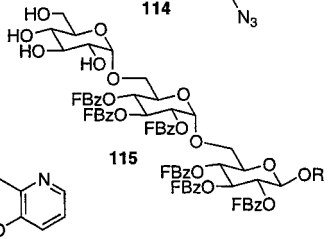
Table 8. Chemical Shifts of Anomeric Protons and Carbons

MOP-Glycosides	^1H (H_1) / ^{13}C (C_1)	MOP-Glycosides	^1H (H_1) / ^{13}C (C_1)	MOP-Glycosides	^1H (H_1) / ^{13}C (C_1)
 46	5.89 / 97.81	 64	6.26 / 93.34	 91	5.96 / 96.12
 56	5.84 / 97.89	 96	6.23 / 93.79	 92	5.93 / 96.52
 59	5.82 / 96.73	 97	6.11 / 94.48	 93	6.16 / 96.14
 60	5.77 / 97.26	 98	6.31 / NA	 94	6.10 / 96.18
 66	6.45 / 95.23	 65	6.75 / 90.60	 99	6.13 / 96.43
 100	6.22 / 93.52	 102	6.57 / 93.96	 101	6.58 / 94.20
 103	6.56 / 93.79				

cis selectivity. The *p*-fluorobenzoate group was found to be particularly suitable as a protective group to deactivate acceptor MOP glycosides because of their better solubility in DMF and ease of deprotection under mild conditions.

To achieve efficient oligosaccharide synthesis, an excess of acceptor is still required, which can be impractical in certain cases. Nevertheless, the products are easily isolated by normal flash chromatography on silica gel column, and the excess amounts

Table 9. Disaccharide and Oligosaccharide Synthesis with MOP Donors and MOP Acceptors

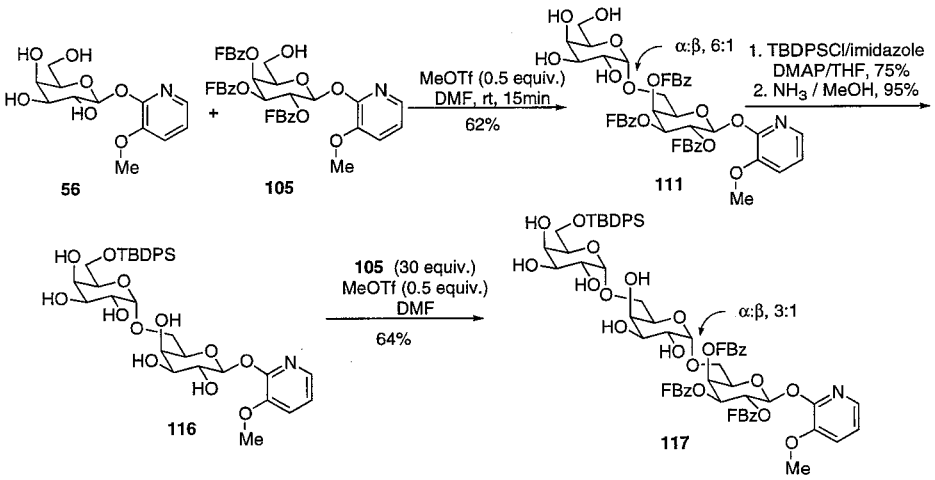
Entry	MOP Donor	Acceptor (equiv.)	Major Product	Catalyst (equiv.)	α : β[a]	Yield (%)
1	**46**	 **104** (20)	 **109**	MeOTf (0.5)	4 : 1	68
2	**56**	 **104** (20)	 **110**	MeOTf (0.5)	6 : 1	65
3	**56**	 **105** (20)	 **111**	MeOTf (0.5)	6 : 1	62
4	**56**	 **106** (28)	 **112**	MeOTf (0.5)	α-only	41
5	**60**	 **107** (N_3) (10)	 **113** (N_3)	TfOH (2.0)	β-only	63
6	**61**	 **107** (N_3) (20)	 **114** (N_3)	TfOH (2.0)	β-only	69
7	**56**	 **108** (30) R= 	 **115**	MeOTf (0.5)	4 : 1	56

[a] Ratio determined by ^{1}H NMR at 300 MHz and confirmed by weights of isolated glycosides whenever possible.

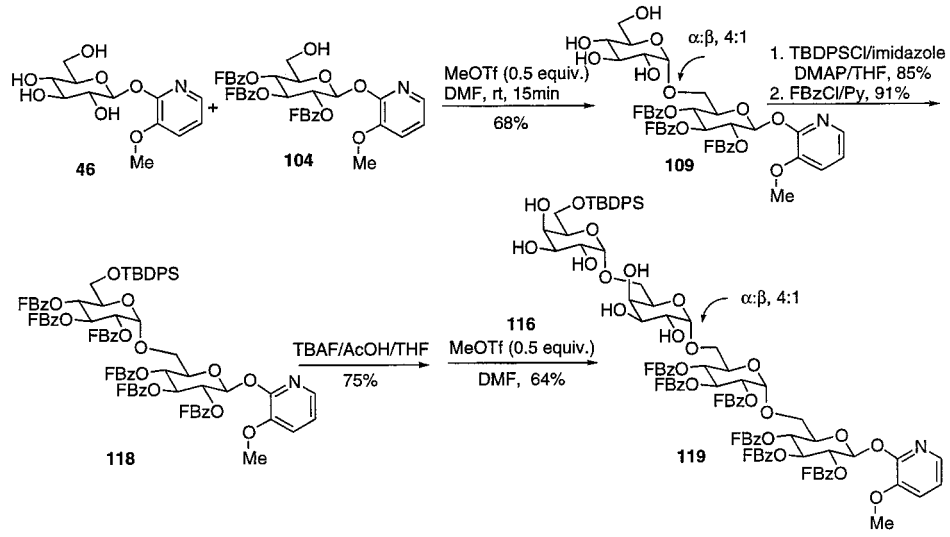
of acceptors can be recovered by using less polar eluents. Alternatively, the products can be isolated after *O*-acetylation.

This method has been successfully extended to the iterative synthesis of oligosaccharides. The disaccharides, derived from selective activation of unprotected MOP glycosyl donors and partially esterified MOP acceptors, can be converted into reactive donors simply by deacylation. The newly generated *O*-unprotected MOP disaccharide donor can be subjected to another cycle of glycosylation by repeating the same process with an appropriate donor. Ex-

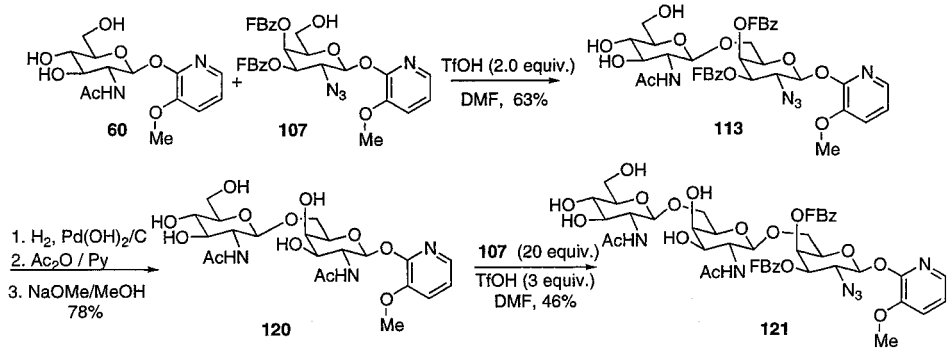
Scheme 14. Iterative Oligosaccharide Synthesis



Scheme 15. Iterative Oligosaccharide Synthesis



Scheme 16. Iterative Oligosaccharide Synthesis



amples of iterative synthesis of tri- and tetrasaccharides with 1,2-*cis* and 1,2-*trans* selectivities are shown in Schemes 14 and 15.

Linear 1,6-α-linked D-gluco and D-galacto oligosaccharides are conveniently and rapidly assembled by using this MOP-selective activation technology. Occasionally the introduction of a TBDPS group in the MOP disaccharide donor as in **116** enhances its solubility. Structures related to **117** and **119** can be found in the glyceroglycolipids.[65]

Biologically relevant 1,2-*trans*-2-acetamido-2-deoxy oligosaccharides such as **121** are easily accessible using a similar strategy by employing 2-azido-2-deoxy and 2-acetamido-2-deoxy derivatives, respectively. As shown in Scheme 16, the glycosylation of 2-azido-3,4-diacylated glycosyl acceptor **107** with an *O*-unprotected 2-acetamido MOP glycosyl donor gave the disaccharide **113** with the desired 1,2-*trans* selectivity in good yield. Subsequently, the azido group was reduced followed by acetylation and de-*O*-acetylation to lead to a reactive 2-acetamido MOP glycosyl donor **120**. The second glycosylation with **107** as acceptor produced the trisaccharide **121** in reasonable yield.

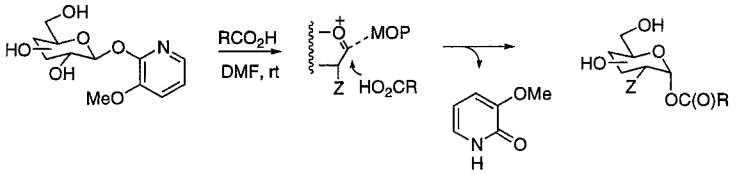
C. Stereocontrolled Synthesis of Glycosyl 1-Carboxylates and Glycosyl Azides

Glycosyl esters are widely distributed in nature.[66] Selective esterification of unprotected aldoses at the anomeric carbon has been reported.[67] For example, esterification of β-D-glucose with active esters derived from 8-hydroxyquinoline gave the corresponding β-D-glucose 1-ester.[67a]

The MOP anomeric activation method was successfully extended to the synthesis of glycosyl 1-carboxylates. Table 10 illustrates examples using the *O*-unprotected MOP D-gluco and D-galacto glycosyl donors **46** and **56**, respectively, in the presence of an excess amount of carboxylic acids *without any promoter*, to give the corresponding 1,2-*cis*-glycosyl carboxylates **122a**−**129a** predominantly even in polar aprotic solvents such as DMF or acetonitrile.[68]

With the corresponding more soluble 6-*O*-*tert*-butyldiphenylsilyl MOP donor, **48**, only a slight excess of carboxylic acid is needed and the reactions can be conducted in dichloromethane as shown in Scheme 17. Treatment of the donor **48** with 1.5 equiv of various carboxylic acids in the presence of MeOTf gave the corresponding 1,2-*cis*-glycosyl carboxylates exclusively in 62−70% yield (α/β, 35:1 to >50:1). This may be attributed to the bulk of the protective group at the C-6 position and shielding the β-face to give preferentially the 1,2-*cis* product in addition to eliminating 1,6-anhydro sugar formation or self-condensation. Of great importance is the application of this method to the synthesis of glycosyl esters corresponding to acids such as palmitic acid and

Table 10. Stereocontrolled Synthesis of Glycosyl 1-Carboxylates

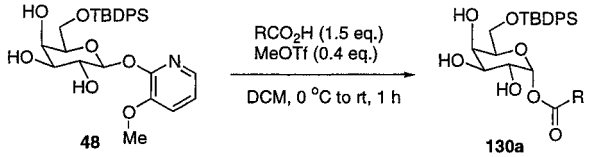


$PhCO_2H$ (20 equiv.)	MeCN [a], 12 h	**122a** (9 : 1, 57%)	*t*-$BuCO_2H$ (200 equiv.)	DMF[a], 12 h	**126a** (20 : 1, 80%)
$PhCO_2H$ (20 equiv.)	MeCN [a], 12 h	**123a** (6 : 1, 58%)	*t*-$BuCO_2H$ (200 equiv.)	DMF[a], 12 h	**127a** (20 : 1, 80%)
$PhCH_2CO_2H$ (20 equiv.)	MeCN [a], 12 h	**124a** (7 : 1, 58%)	(200 equiv.)	MeCN [a], 12 h	**128a** (30 : 1, 80%)
$PhCH_2CO_2H$ (20 equiv.)	MeCN [a], 12 h	**125a** (6 : 1, 60%)	(200 equiv.)	MeCN [a], 12 h	**129a** (30 : 1, 90%)

[a] Reaction done at 45 °C

aspirin.[68] Thus, the method allows the solubilization of lipophilic compounds in water as their esters and potential applications to drug delivery.[69] Analogous reactions with MOP donors derived from *N*-acetyl neuraminic acid methyl ester gave the corresponding 2-esters as single anomers.[70]

Scheme 17. Esterification Using 6-*O*-TBDPS MOP Donor[a]



[a] RCO_2H = acetic acid, pivalic acid, benzoic acid, phenylacetic acid, *trans*-2-pentenoic acid, palmitic acid, *N*-Boc-L-phenylalanine, acetyl salicylic acid.

Treatment of unprotected MOP glycosyl donor **46** with excess trimethylsilyl azide in DMF containing TMSOTf led to the formation of crystalline α-D-glucopyranosyl azide in 95% yield.[65] It is possible that some or all of the hydroxyl groups of **46** are silylated in the presence of excess reagent and then cleaved during workup. In contrast to other methods which afford the *β*-azide predominantly[49] or exclusively,[50] the MOP donor **46** gives the α-anomer, possibly via a stereoelectronically favored attack of azide ion in an S_N2-like mechanism (Scheme 12).

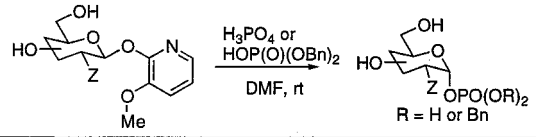
D. Stereocontrolled Synthesis of Glycosyl 1-Phosphates and Glycosyl Nucleotides

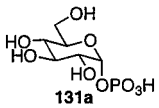
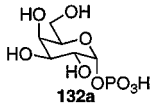
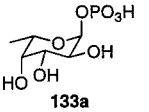
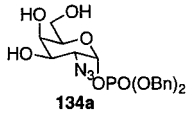
Glycosyl 1-phosphates and sugar nucleotides are of major interest due to the vital role that these compounds play in biological processes.[71] In biosynthesis, glycosyl phosphates are key intermediates to nucleotide diphosphate sugars which act as glycosyl donors in the presence of glycosyl transferases for the construction of various glycosidic linkages. A number of synthetic approaches, including enzymatic and chemical methods for the preparation of glycosyl 1-phosphates, have been developed.[72] However, these methods often involve tedious purification processes. Nevertheless, the enzymatic approach to glycosyl 1-phosphates described by Whitesides[73] can be done on a reasonably large scale to yield products with a purity in the range of 80−85%. The chemical syntheses are based on multistep procedures reported many years ago involving protection and deprotection.[74]

One of the major attributes of the MOP glycosyl transfer method is the feasibility of stereocontrolled glycosidic bond formation *without the need for protective groups*, reminiscent of enzyme-mediated reactions. MOP technology for anomeric activation has also proved its versatility in direct anomeric phosphorylation with or without protective groups in the glycosyl donors.[75]

Examples of the successful stereocontrolled phosphorylation of *O*-unprotected MOP glycosyl donors to afford the corresponding anomeric 1-phosphates are shown in Table 11. Treatment of the *β*-D-glucopy-

Table 11. Stereocontrolled Synthesis of Glycosyl-1-phosphates



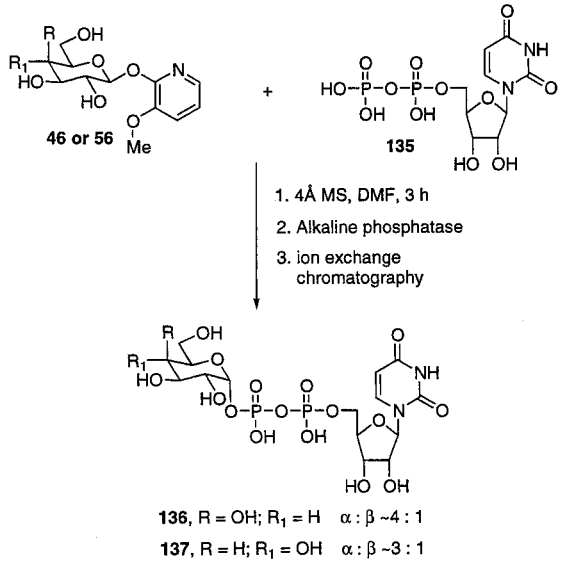
Acids (equiv.)	Conditions	Products (α / β, yield)
H_3PO_4 (7 equiv.)	DMF rt, 3 h	 **131a** (only α, 66%)
H_3PO_4 (7 equiv.)	DMF rt, 3 h	 **132a** (only α, 65%)
H_3PO_4 (7 equiv.)	DMF rt, 3 h	 **133a** (only α, 60%)
$HOP(O)(OBn)_2$ (7 equiv.)	CH_3CN rt, 2 days	 **134a** (only α, 64%)

ranosyl, β-D-galactopyranosyl, and α-L-fucopyranosyl MOP donors **46**, **56**, and **57**, respectively with 7 equiv of phosphoric acid in DMF as solvent led to corresponding α-anomeric 1-phosphates **131a**−**134a** in good yield and excellent stereoselectivity. In the case of 2-azido-2-deoxy-α-D-galactopyranosyl MOP **59**, a longer reaction time was required due to the presence of the electron-withdrawing azido group at the C-2 position. Interestingly, higher stereoselectivity of phosphorylation was achieved when dibenzyl phosphate was used instead of the free acid to give the corresponding α-1-dibenzyl phosphate triester which was then readily converted into α-D-galactosamine 1-phosphate by hydrogenation. Using the neighboring group participation strategy, β-L-fucosyl 1-phosphate was prepared in 51% yield from MOP 2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl donor.[76]

MOP donor technology also offers direct access to sugar nucleotides.[77] As shown in Scheme 18, condensation of the *O*-unprotected MOP donors, **46** and **56**, with 2 equiv of uridine 5′-diphosphate (UDP) free acid, freshly generated from the corresponding commercially available trisodium salt in DMF, gave the desired UDP-galactose **136** and UDP-glucose **137**, respectively, predominantly as α-anomers. High purity of the sugar nucleotides was achieved by a two-step procedure. First, the residual UDP in the reaction mixture was separated after hydrolysis with the presence of alkaline phosphatase. A subsequent purification by ion-exchange chromatography gave the desired nucleotides as white powders (∼50−60%, $\alpha/\beta = 4:1$).[77]

As in the *O*-glycosylation reactions, phosphorylation with *O*-unprotected MOP glycosyl donors most

Scheme 18. Stereocontrolled Synthesis of Uridine-5′-diphosphogalactose and Uridine-5′-diphosphoglucose



likely proceeds via an S_N2-like mechanism in which the MOP leaving group is activated by protonation of the nitrogen atom in the pyridyl ring by phosphoric acid or UDP free acid. It is not clear yet whether an intermolecular or an intramolecular reaction is involved. Further mechanistic studies will certainly lead to an improvement of anomeric selectivity.

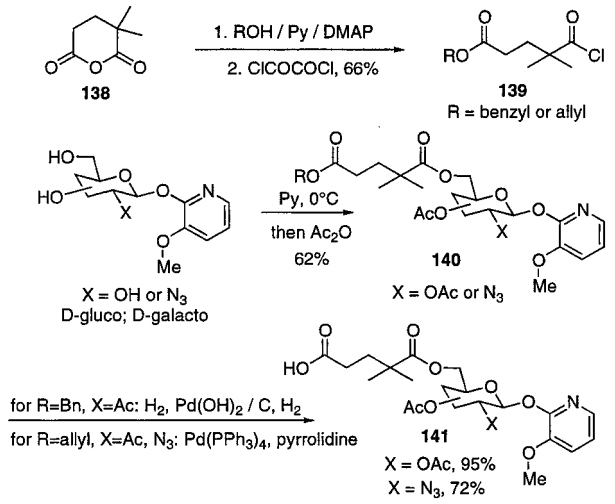
4. Solid-Phase Synthesis Using MOP Donors and Acceptors

One of the revolutionary achievements in chemical synthesis in the last century was the introduction of the Merrifield solid-phase technique,[78] which has seen considerable advances since its milestone announcement in 1963. Automated solid-phase syntheses of polypeptides and oligonucleotides are widely practiced today. In contrast, the assembly of complex carbohydrate oligomers on solid support is still at a nascent stage.[79] The challenges listed in section II loom ever so menacingly when considering solid-phase oligosaccharide synthesis. In particular, protective group compatibilities in the donor and acceptor emerge as major obstacles, especially when an iterative method of oligosaccharide assembly is contemplated. Considering this feature alone, it is clear that anomeric activation utilizing *O*-unprotected MOP-glycosyl donors could offer a viable solution to the challenges of solid-phase glycoside synthesis.[80]

A. Linking Strategy

Considering the conditions for activation of MOP donors, the following criteria should be fulfilled when considering solid-phase synthesis: (a) ready attachment (loading) to solid support in high yield; (b) compatibility with the anomeric activation conditions; (c) stability under the conditions of protection and deprotection of glycosyl donors and iterative assembly; (d) linker should not deactivate the anomeric MOP leaving group; (e) readily cleavable under appropriate conditions to liberate glycosides or oligosaccharides from the solid support.

Scheme 19. Attachment of a Designed Linker to MOP Glycosyl Donors



2,2-Dimethyl glutaric acid was chosen as a linker for our exploratory studies. As shown in Scheme 19, the regioselective ring opening of commercially available 2,2-dimethyl glutaric anhydride by benzyl alcohol or allyl alcohol followed by treatmentwith oxalyl chloride gave the acid chloride **139** in good overall yield. Regioselective esterification by the sterically hindered acid chloride at the *O*-6 position of the MOP glycosyl donor was then achieved in pyridine at low temperature. Removal of the benzyl ester from **140** by hydrogenolysis (for X = OAc), or with $Pd(PPh_3)_4$ (for X = N_3) afforded the corresponding free acids represented by **141** (Scheme 19). Further manipulations of the distal carboxylic acid led to the activated pyridylthio ester **142** (Scheme 20). Attachment to aminomethyl polystyrene gave **143** in almost quantitative yield. The polymer-bound MOP donor was then selectively de-*O*-acetylated by exposure to a solution of ammonia in MeOH. On the basis of this method, a variety of polymer-bound MOP glycosyl donors such as **144**−**147** were prepared.

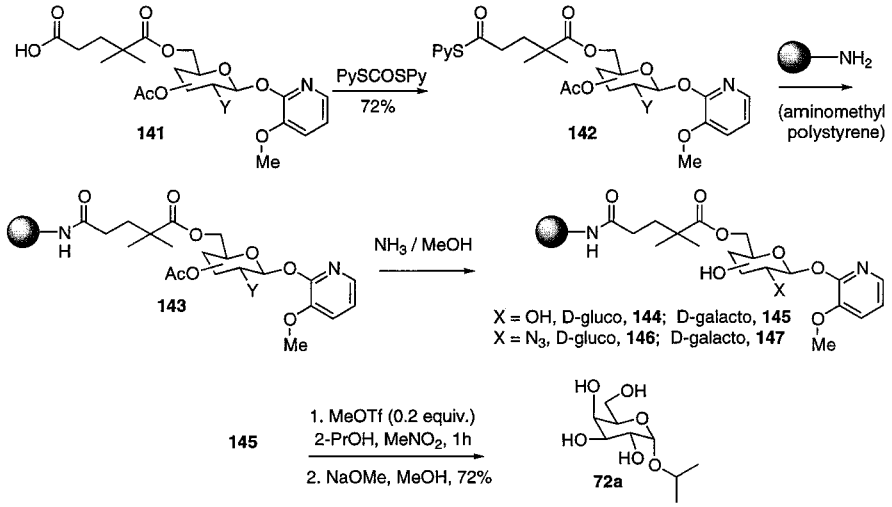
It is also possible to link MOP donors as resin-bound 6-diisopropylsilyl ethers[81] as shown in Scheme 21. Thus, treatment of MOP donors **56** or **59** (Table 4) with the diisopropyl chlorosilane resin[79a] in DMF led to the corresponding ethers **148** and **149** with excellent loading (∼0.8 mmol/mol).

B. Synthesis of O-Glycosides and Oligosaccharides on Solid Support

Anomeric activation of the polymer-bound MOP donor **144** and glycoside synthesis was achieved by treatment of the resin with 0.2 equiv of MeOTf in a 1:1 mixture of 2-propanol and $MeNO_2$ for 1 h (Scheme 20). After filtration and washing, the desired *O*-glycoside was cleaved from the resin with NaOMe and isolated as an anomeric mixture (8: 1 α/β) in good yield after acetylation. This compares very favorably with the analogous reaction in solution (Table 1, entry 3). The reaction could be performed equally well in other solvents, such as dichloromethane, acetonitrile, and DMF, but with lower α-selectivity. 2-Propyl glycosides **72a** and **73a** were also prepared from the silyl-ether-bound MOP donors **148** and **149**, respectively[79a] (Scheme 21).

The synthesis of disaccharides was performed in the presence of a large excess of sugar acceptor **78** as shown in Table 12. The polymer-bound MOP donors **144**, **145**, and **147** were activated with 0.7 equiv of MeOTf, and the reaction was conducted for 1−4 h depending on the nature of the glycosyl donor used. Excess sugar acceptor was readily recovered by

Scheme 20. Coupling to the Solid Support



Scheme 21. Silyl Ether Linkage

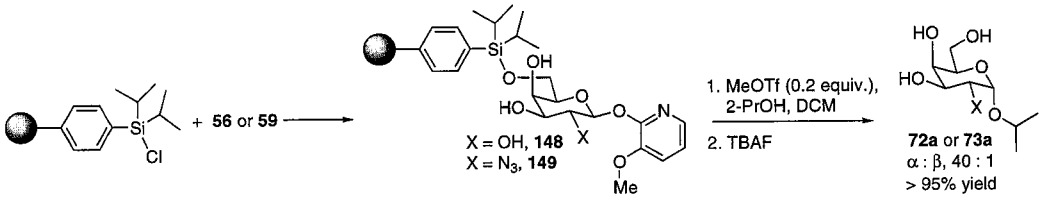
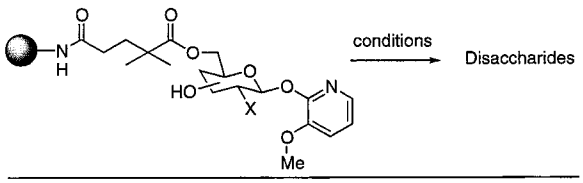
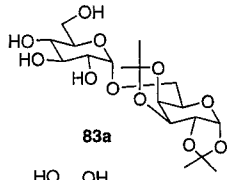
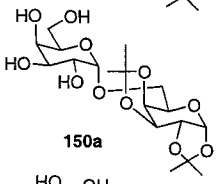
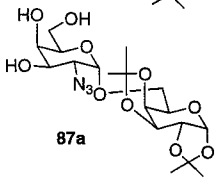


Table 12. Formation of Disaccharides on Solid Support[a]



Entry	Major Product	α : β	Yield (%)
1	 **83a**	4 : 1	62
2	 **150a**	3 : 1	54
3	 **87a**	3 : 1	56

[a] Conditions: (1) ROH (100 equiv)/MeOTf (0.7 equiv), Me-HO_2, rt, 1−4 h; (2) NaOMe/MeOH/DCM.

filtration upon completion of the reaction. The desired disaccharides were then cleaved from the resin and isolated predominantly as α-isomers in 54−62% yield. In all cases, the corresponding aldoses were the only byproducts isolated, indicating that the yield could be potentially improved by avoiding adventious moisture in the reaction media. It is important to mention that the glycosylations can be readily monitored by TLC upon the release of the MOP leaving group 3-methoxy-2-(1*H*)-pyridone in solution (Scheme 12).

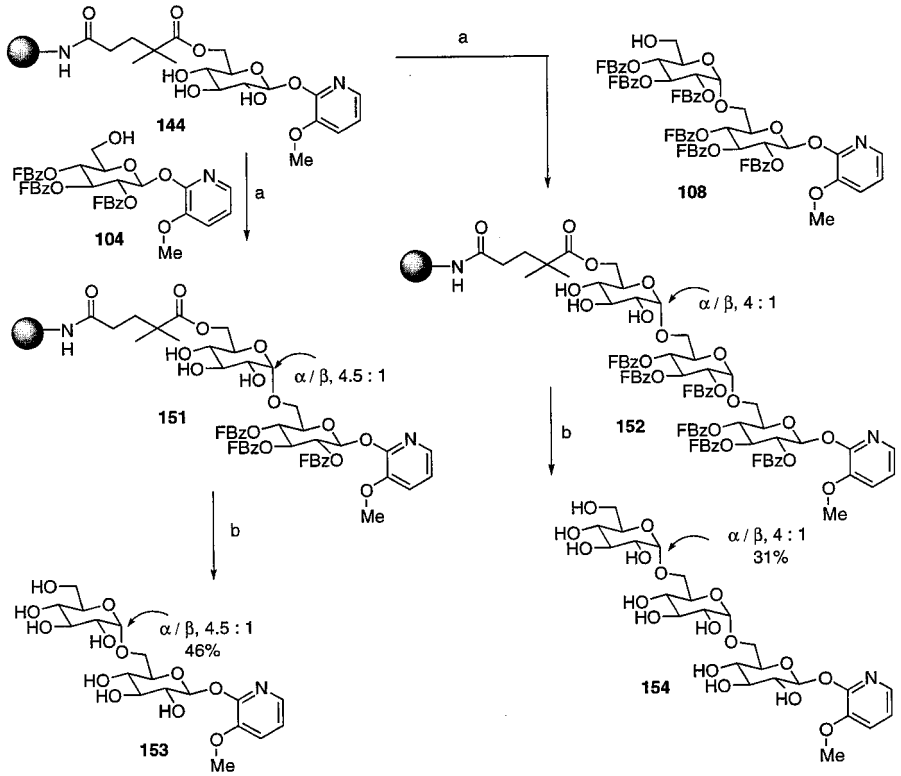
The potential for iterative oligosaccharide assembly is illustrated in Scheme 22. As in the solution method, the partially acylated MOP glycosides, such as **104** and **108**, were used as the glycosyl acceptors. Activation of the polymer-bound MOP donor **144** was achieved in DMF as solvent using 4 equiv of TfOH in the presence of 20 equiv of the acceptor. This process was repeated twice in order to push the reaction to completion and to afford the polymer-bound MOP saccharides **151** and **152**, respectively (Scheme 22). The desired disaccharide and trisaccharide were obtained upon cleavage from the resin in 46% and 31% yield, respectively.

Operationally, solid-phase oligosaccharide synthesis based on MOP donor/acceptor methodology relies on a two-step process. Thus, an *O*-unprotected polymer-phase bound MOP donor such as **144** is coupled with a partially esterified MOP acceptor such as **104** or **108**. Selective removal of the ester (or related groups) from the new saccharides generates a new *O*-unprotected MOP donor to engage in a subsequent iteration as shown in Scheme 22. In principle, the polymer-bound MOP *O*-acylated donors **151** and **152** can be deacylated and the iteration continued with appropriate alcohol acceptors.

VII. Conclusion

We have described successful examples of glycoside and oligosaccharide synthesis using *O*-unprotected

Scheme 22. Solid-Phase Synthesis of Oligosaccharides[a]



[a] Reagents and conditions: (a) acceptor (20 equiv), TfOH (4 equiv), DMF, rt, 7 h; (b) NaOMe/MeOH.

glycosyl donors with a 3-methoxy-2-pyridyloxy (MOP) leaving group at the anomeric carbon. *O*-Unprotected MOP glycosyl donors can be readily activated by MeOTf and other promoters in the presence of variable excesses of acceptors, forming 1,2-*cis*-glycosides as major products. *O*-Unprotected MOP 2-acetamido-2-deoxy-glycosyl donors give exclusively 1,2-*trans*-glycosides as a result of neighboring group participation via an oxazolinium ion. The selective activation of *O*-unprotected MOP donors relative to *O*-acyl MOP acceptors leads to a method for the iterative assembly of oligosaccharides with minimal functional group manipulation. Direct application to solid-phase synthesis has been demonstrated. Other technologies such as combinatorial chemistry,[82] protein glycosylation,[83] and related biologically relevant processes[6] can also be envisaged using *O*-unprotected MOP glycosyl donors.

MOP technology for glycosyl transfer has also proved its versatility in stereocontrolled esterification and phosphorylation, leading to glycosyl 1,2-*cis*-1-carboxylates or glycosyl 1,2-*cis*-glycosyl-1-phosphates in one step. The method is also useful in the synthesis of sugar nucleotides such as UDP-Glc and UDP−Gal in one step using the corresponding *O*-unprotected MOP donors. The design of MOP donors, their chemical reactivity, selectivity, and versatility also have been extensively studied using *O*-protected derivatives such as *O*-benzyl ethers and esters.[84,85] Applications to the synthesis of 1,2-*cis*- and 1,2-*trans*-glycosides and oligosaccharides using these *O*-protected MOP donors have been amply demonstrated. The versatility and chemical modulation of the reactivity of MOP donors can be further validated in conjunction with another anomeric leaving group, the 2-pyridylthiocarbonate (TOPCAT).[37,86] Using selective activation, it is possible to utilize MOP and TOPCAT glycosides of *O*-protected sugars to assemble biologically relevant oligosaccharides.[65]

This article started by stating that "half of sugar chemistry resides at the anomeric carbon atom". The exploration of anomeric leaving groups, as exemplified by MOP and TOPCAT motifs[37,86] in conjunction with glycosyl donors, has shown the potential of creative design that capitalizes on functional group reactivities.[87] Clearly, the area remains fertile and challenging in our quest to approach the power of enzymatic reactions in glycosyl transfer reactions.

VIII. Acknowledgments

We thank NSERC for generous financial assistance through the Medicinal Chemistry Chair program.

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CR9903454